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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,823	09/23/2003	Qun Sun	6750-157-999	6999

20583 7590 10/28/2005

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,823	SUN ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-133* is/are pending in the application.

4a) Of the above claim(s) *20-95,97-100,102-105,107-110 and 114-125* is/are withdrawn from consideration.

5)☒ Claim(s) *1-19,96 and 111-129* is/are allowed.

6)☒ Claim(s) *101,106 and 130-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-19, 96, 101, 111-113 and 126-133 in the reply filed on 8/23/2005 is acknowledged.

Claims 20-95, 97-100, 102-105, 107-110 and 114-125 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Although applicants traversed the restriction requirement , they have not provide any arguments to show the restriction is improper.

The requirement is still deemed proper and is therefore made FINAL.

Applicants have pointed out the Formula VII is not listed in the instant restriction requirement . As applicants might have noticed the claims 126 1-33 include the claim 127 and its dependent claims. So omission of formula VII is inadvertent and does not change the scope of claims included.

For the record, revised restriction requirement is presented below:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-19, 96, 101, 106, 111-113 and 126-133, drawn to compound of formula I or compound of formula VI or Formula VII wherein Ar_1 is pyridine, namely piperidinopyridine, composition and method of use, classified in class 544, subclass 360, class 514, subclass 252.13.

II. Claims 20-38, 97, 102, 107, 114-116 and 126-133, drawn to compound of formula II or compound of formula VI or Formula VII wherein Ar_1 is pyrazine, namely piperidinopyrazine, composition and method of use classified in class 544, subclass 357, class 514, subclass 252.11.

III. Claims 39-57, 98, 103, 108, 117-119 and 126-133, drawn to compound of formula III or compound of formula VI or Formula VII wherein Ar_1 is pyrimidine, namely piperidinopyrimidine, composition and method of use, classified in class 544, subclass 322, class 514, subclass 252.14.

IV. Claims 58-76, 99, 104, 109, 120-122 and 126-133, drawn to compound of formula IV or compound of formula VI or Formula VII wherein Ar_1 is pyridazine, namely piperidinopyridazine, composition and method of use, classified in class 544, subclass 238, class 514, subclass 252.01.

V. Claims 77-95, 100, 105, 110, 123-133, drawn to drawn to compound of formula V or compound of formula VI or Formula VII wherein Ar_1 is thiadiazole, namely piperidinothiadiazole, composition and method of use, classified in class 544, subclass 367, class 514, subclass 253.10.

Claims 1-19, 96, 101, 111-113 are under consideration.

Information Disclosure Statement

References cited in the Information Disclosure Statement , filed on 8/23/2005, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 101, 106 and 130-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain due to headache or arthritis, does not reasonably provide enablement for treating any or all pain originating from various diseases generically embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

First of all, instant claims are reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification.

In the instant case, it appears that, because the instant compounds interact with vanilloid receptor and that vanilloid receptors are present in the human body, it is recited that any or all pain can be treated with the instant compounds for which there is no adequate written description and enabling disclosure. Furthermore, references provided

in the Information Disclosure Statement either alone or in combination do not provide support for the scope of generically embraced in the instant claims.

The scope of the claims includes treating any or all pain arising from various diseases and disorders as mediated by vanilloid receptor for which there is no enabling disclosure. More specifically the scope of these claims includes treating pain associated with an inflammatory disease such as organ transplant rejection; reoxygenation injury resulting from organ transplantation , transplantation of the heart, lung, liver, or kidney', cllronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resoption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inthmmatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis', autoimmune diseases, including Type I and Type 11 diabetes mellitus', diabetic

complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a Candida infection or necrobiosis lipoidica diabeticoruml; immune-complex vasculitis, and systemic lupus erythematosus (SLE), inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer and many others., which are not adequately enabled solely based on the inhibiting vanilloid receptor activity of the compounds provided in the specification at pages 1-8 and 147-150. The instant compounds are disclosed to have inhibiting vanilloid receptor activity and it is recited that the instant compounds are therefore useful in treating any or all diseases where vanilloid receptor activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. The scope of the claims involves all of the thousands of compounds of instant claims as well as the thousand of diseases embraced by the terms inflammatory diseases, non-vascular syndromes etc

Inflammation is a process that can take place in virtually any part of the body.

There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

Furthermore, , treatment of individual disease/disorder need not extrapolate to treating any or all generic diseases.

For example, although there are compounds for treating headache, they are not found to treat any or all pain such pain suffered by cancer patients.

No compound has ever been found to treat all types of pain. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Dogurl et al., Di Marzo et al., and Foley cited in the Information Disclosure Statement which indicative of further future experimentation. See also Valenzano et al. Curr. Med. Chem. 3185-3202, 2004 (PubMed Abstract provided), and Szallasi et al, Journal of Medicinal Chemistry 47(20): 2716-2723, 2004.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating any or all pain from various diseases and disorders that require inhibiting vanilloid receptor activity.

2) The state of the prior art: Recent publications expressed that treating disease or disorders by the inhibition of vanilloid receptor is still exploratory. See Valenzano et al., as well as Szallasi et al. cited above. Note all these references state the vanilloid

receptor-mediated diseases/disorders in general are at best in the early experimental stage and needs further exploratory studies.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all pain arising from any or all diseases or disorders of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all pain and the state of the art is that the effects of inhibiting vanilloid receptor activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all diseases and disorders related vanilloid receptor.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general,

and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Allowable Subject Matter

Claims 1-19, 96 and 111-129, barring finding of any prior art in a subsequent search, would be allowed.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

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10/16/2005